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Rubella Seroepidemiology and Catch-up Immunization among Pregnant Women in Taiwan: Comparison between Women Born in Taiwan and Immigrants from Six Countries in Asia

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Abstract. Rubella vaccination in Taiwan started in 1986; mass vaccination was introduced into the national immunization program in 1992. In recent years, 17–31% of all marriages in Taiwan have been between Taiwanese men and foreign women. The aim of this study was to analyze rubella seroepidemiology and the rate of catch-up immunization in women. We recruited 10,089 pregnant women, including 1,920 immigrants, who had received prenatal examinations during 1999–2006. The rates of seronegativity among global, Taiwan-born, and non–Taiwan-born pregnant women were 14.0%, 11.9%, and 23.1%, respectively. The seronegativity of rubella antibodies decreased from 28.2% for Taiwan-born women born before September 1971 to 8.0% for those born thereafter. The rates of rubella catch-up immunization among global, Taiwan-born, and non–Taiwan-born pregnant women were 28.6%, 20.5%, and 42.2%, respectively. Our results suggest that substantial numbers of older Taiwan-born women and immigrant women remain susceptible to rubella infection.

INTRODUCTION

Rubella infection is caused by an RNA virus. The symptoms of rubella infection include a rash, low-grade fever, arthralgia, and lymphadenopathy. In most cases, the disease is self-limiting and rarely causes complications. Nevertheless, it causes congenital rubella syndrome (CRS) when the infection occurs during the first trimester of gestation. Complications of CRS may include miscarriage and severe abnormalities of the fetus, such as cataracts, retinopathy, heart defects, neurological deficits, and deafness.[1,2] No antiviral drugs are available for treating rubella or preventing transmission to the fetus. Vaccination programs are regarded as an effective tool to eliminate rubella and congenital rubella.

In Taiwan, rubella vaccination began in 1986 (Table 1). Female students in their third year of junior high school were immunized against rubella during 1986–1991. From 1992 through 1994, single doses of measles, mumps, and rubella (MMR) vaccine were given to all junior high school students, elementary school students, and preschool children. The vaccination program has also been available since 1987 to all women of childbearing age. Mass vaccination, in which single doses of MMR were given to 15-month-old toddlers, was introduced into the national immunization program in 1992. Starting in 2001, a booster dose of MMR was administered to all students in their first year of elementary school. The purpose of the vaccination program was to provide rubella vaccinations to the female population born after September 1971 and to both sexes born after September 1976.[3]

Rubella is classified as a category 2 reportable disease; samples of reported cases must be sent to Center for Disease Control (CDC) laboratory in Taiwan for confirmation. According to the statistics of CDC, the confirmed number of rubella cases during 1999–2007 ranged from 2 to 54/year. The annual incidence rate ranged from 0.09 to 2.35/one million population during 1999–2007.[4] During 1994–2008, CRS developed in five neonates: two were contracted locally and the other three were contracted overseas to children born to immigrant women from Indonesia, Vietnam, and China, respectively.[5]

Most countries in Asia have not introduced rubella vaccination into their national immunization programs.[6] Over the past decade, marriages between Taiwanese men and foreign women from China and Southeast Asian countries (including Vietnam, Indonesia, the Philippines, Thailand, and Malaysia) have become commonplace.[7] During 2002–2006, these marriages accounted for 28%, 31%, 23%, 20%, and 17% of all marriages, respectively, with children from these marriages accounting for 12%, 13%, 13%, 13%, and 12% of all neonates, respectively.[8] Therefore, the presence of these new immigrants from China and Southeast Asian countries might have some effect on the effectiveness of the rubella immunization program in Taiwan.

During 1986–1991, the vaccination coverage rate among junior high school girls was 98%.[9] According to CDC statistics, in 2006, the coverage rate for single doses of MMR was 95.9%.[10] Several recent reports have described the prevalence of rubella antibodies in different areas in Taiwan. Two of them examined urban vaccination status in northern Taiwan (Taipei), one by Wang and others in 2004[11] and the other by Lu and others in 2003–2005.[12] A third study, conducted by Su and Guo in 2000,[13] investigated the vaccination status in rural areas of southern central Taiwan, especially Tainan County. Another study, conducted by Tseng and others in 1999–2002,[14] studied the prevalence of vaccination in rural areas of southern Taiwan (Pingtung). To the best of our knowledge, there are no reports of investigations into catch-up immunization in women of childbearing age who are susceptible to rubella infection. The aim of this study was to compare the seroprevalence of rubella antibodies in women of different ages and from various birthplaces and to determine their catch-up immunization status.

MATERIALS AND METHODS

Subjects. This study recruited 10,089 pregnant women, including 1,920 immigrants from China, the Philippines, Cambodia, Indonesia, Thailand, and Vietnam. All of these pregnant women received routine prenatal examinations at Fooyin University Hospital, a regional hospital that specializes

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TABLE 1
Rubella and MMR vaccination programs in Taiwan*

Period	Type of vaccine	Population	Affected cohort
1986–1991	Rubella	Girls in the third year of junior high school (15 years of age)	9/1971–8/1976
1992–1994	MMR	All third-grade students of junior high school (15 years of age)	9/1976–8/1979
		All elementary school students (7–12 years of age)	9/1979–8/1985
		Preschool children	9/1985–8/1990
1992–8/2001	MMR	Children: 15 months of age	9/1990–8/1994
9/2001–present	MMR	First dose: 15 months of age	9/1994–present
		Booster dose: first year of elementary school	
1987–6/2001	Rubella	Women of child-bearing age	Child-bearing age
7/2001–present	MMR	Women of child-bearing age	Child-bearing age

*Adapted from the report of the Center for Disease Control, Taiwan.[3]
MMR = measles, mumps, and rubella.

in obstetric health care in Southern Taiwan, during 1999–2006, when the rubella antibodies test was already a compulsory checkup item during routine prenatal examinations. Therefore, data regarding the prevalence of rubella antibodies for all of pregnant women recruited into this study were obtained without the need for additional blood collection. The study protocol was reviewed and approved by the Fooyin University Hospital Ethics Review Board.

Catch-up immunization. To calculate the rate of catch-up immunization in childbearing women, we compared the results from the rubella antibodies tests of women who had consecutive pregnancies during 1999–2006. Because there was only one confirmed case of rubella in Pingtung County during this period,[4] we considered the seropositive conversion of rubella antibodies in these women to be the result of immunization.

Serological tests. IgG antibodies against rubella were measured from blood samples collected from pregnant women during the early second trimester prenatal examinations. These antibodies were analyzed by using a microparticle enzyme immunoassay and an AsXYM analyzer (Abbott Laboratories, Abbott Park, IL). Serum IgG levels ≥ 10 IU/mL were considered seropositive or immune; those < 10 IU/mL were considered seronegative, susceptible, or non-immune.[11]

Statistical analysis. Subjects were categorized by nationality and sub-categorized by specific periods of time. The differences between Taiwanese and immigrant women were compared using a chi-square test, and the odds ratio (OR) was calculated for seronegativity. To compare seronegativity of rubella antibodies for different age and birthdate cohorts, we stratified our data with respect to different periods during 1999–2006. *P* values less than 0.05 were considered significant. Data were analyzed using SPSS version 10.0 software for Windows (SPSS, Inc., Chicago, IL).

RESULTS

A total of 10,089 pregnant women received routine blood tests during their antenatal visits during 1999–2006 at Fooyin University Hospital. Among them, 8,169 were Taiwanese women and 1,920 (19.0%) were immigrant women. The global rubella seronegativity was 14.0% among these pregnant women. The rubella seronegativity for Taiwan-born and non–Taiwan-born pregnant women was 11.9% and 23.1%, respectively. The seronegativity by country of origin was 24.9% for China, 20.6% for the Philippines, 11.8% for Cambodia, 16.8% for Indonesia, 4.8% for Thailand, and 24.5% for Vietnam. Thus, pregnant women born in China, the Philippines, Indonesia, and Vietnam had the highest seronegativity values (Table 2).

To determine the difference in seronegativity rates of rubella antibodies between the Taiwan-born and non–Taiwan-born women, we stratified the groups (Table 3) in terms of the year of birth and also compared the data using a cutoff time set at September 1971, the month when the mass vaccination program was implemented. The immigrant group had significantly higher rubella seronegativity (OR = 2.24, 95% confidence interval [CI] = 1.98–2.54) relative to the Taiwanese women. The percentages of Taiwan-born women lacking rubella antibodies in the birth groups pre-1966, 1966–1970, 1971–1975, 1976–1980, and post-1980 were 28.9%, 29.4%, 9.2%, 6.8%, and 10.8%, respectively. Older Taiwanese pregnant women seemed to have higher chances of being seronegative. The rubella seronegativity rate decreased from 28.2% for Taiwanese women born before September 1971 to 8.0% for those born after September 1971. In the birth groups born before 1966, there were no statistically significant differences between Taiwan-born and non-Taiwan–born pregnant women (OR = 1.23, 95% CI = 0.48–3.17). In the birth group 1966–1970, the pregnant women born in Taiwan had higher

TABLE 2
Rubella seronegativity among pregnant women in Fooyin University Hospital, Taiwan, 1999–2006

Group	1999–2000	2001–2002	2003–2004	2005–2006	Total	No. of seronegative cases	Percentage of seronegative cases 95% confidence interval
Total	2,524	2,568	2,568	2,429	10,089	1,414	14.0 (13.3–14.7)
Taiwan born	2,440	2,095	1,797	1,837	8,169	970	11.9 (11.2–12.6)
Non–Taiwan born	84	473	771	592	1,920	445	23.1 (21.3–25.1)
China	2	59	129	108	305	76	24.9 (20.1–29.8)
The Philippines	25	20	10	8	63	13	20.6 (10.6–30.6)
Cambodia	4	23	13	11	51	6	11.8 (2.9–20.6)
Indonesia	25	71	57	31	184	31	16.8 (11.4–22.3)
Thailand	7	4	6	4	21	1	4.8 (−4.3–13.9)
Vietnam	12	294	554	429	1,289	318	24.5 (22.3–27.0)
Others*	2	2	2	1	7	0	0

*Including Malaysia and Myanmar.

TABLE 3
Rubella seronegativity by year of birth among Taiwan-born and non–Taiwan-born pregnant women, Taiwan

Characteristic	Taiwan	Non-Taiwan	Non-Taiwan vs. Taiwan	
	No. negative/total (%)	No. negative/total (%)	Odds ratio (95% confidence interval)*	*P*
Total	970/8169 (11.9)	445/1920 (23.1)	2.24 (1.98–2.54)	< 0.001
Year of birth				
< 1966	76/263 (28.9)	7/21 (33.3)	1.23 (0.48–3.17)	0.417
1966–1970	303/1030 (29.4)	15/86 (17.4)	0.51 (0.29–0.90)	0.010
1971–1975	216/2340 (9.2)	43/248 (17.3)	2.07 (1.44–2.95)	< 0.001
1976–1980	196/2885 (6.8)	145/643 (22.6)	4.00 (3.16–5.05)	< 0.001
> 1980	179/1615 (10.8)	235/922 (25.5)	2.81 (2.27–3.49)	< 0.001
Born before and after vaccination				
Before 9/1971	442/1568 (28.2)	25/122 (20.5)	0.66 (0.42–1.03)	0.067
9/1971 and after	528/6601 (8.0)	420/1798 (23.4)	3.51 (3.05–4.04)	< 0.001

*Taiwan-born pregnant women were used as the reference group.

seronegativity than did those born elsewhere (OR = 0.51, 95% CI = 0.29–0.90). In contrast, the pregnant immigrant women in birth groups 1971–1975 (OR = 2.07, 95% CI = 1.44–2.95), 1976–1980 (OR = 4.00, 95% CI = 3.16–5.05), and post-1985 (OR = 2.81, 95% CI = 2.27–3.49) had higher chances of being seronegative, compared with those born in Taiwan.

We also obtained data for women who returned to the obstetrical service at Fooyin University Hospital for subsequent pregnancies during 1999–2006. Among them, 241 pregnant women did not have rubella antibodies on their initial antenatal visit. We followed-up on the rubella antibody results of their subsequent pregnancies and found a global rubella seroconversion rate of 28.6% (69 of 241). The rubella seroconversion rate was 20.5% (31 of 151) in Taiwan-born women and 42.2% (38 of 90) in non–Taiwan-born women (Table 4). Although the catch-up immunization rate was low for both indigenous and foreign-born women, it was higher among immigrant women than among Taiwan-born women.

DISCUSSION

Among those born before the onset of mass vaccination in Taiwan, Taiwan-born pregnant women displayed similar and sometimes higher seronegativity values relative to those of immigrant pregnant women. A distinct change appeared in the data for younger pregnant women born after the implementation of the national rubella vaccination program. In the birth groups 1971–1975, 1976–1980, and post-1980, Taiwan-born pregnant women had lower seronegativity rates than did non–Taiwan-born pregnant women (Table 3). The rate of seronegativity for pregnant women who were born in Taiwan before September 1971 (28.2%) decreased substantially for those born thereafter (8.0%). This observation can be explained by considering the fact that the rubella and MMR vaccination programs first introduced in 1986 would have immunized women born after September 1971 (Table 1). This finding also shows the efficacy of the compulsory vaccination program.

TABLE 4
Seroconversion of rubella antibodies in pregnant women whose first antenatal screening results were susceptible, Taiwan

Group	No. positive/total	Seroconversion, % (95% confidence interval)	*P*
Taiwan born	31/151	20.5 (14.1–27.0)	
Non–Taiwan born	38/90	42.2 (32.0–52.4)	< 0.001
Total	69/241	28.6 (22.9–34.3)	

The seronegativity rates found in our present study were higher than those reported in studies of other areas of Taiwan. For local women born after 1971 (< 15 years of age in 1986), Wang and others[11] and Lu and others[12] reported seronegativity rates of 2.7% (23 of 867) and 4.4% (76 of 1,717), respectively, in the Taipei urban area. The seronegativity was 4.0% (39 of 985) in the study of Su and Guo, which was conducted in rural areas of southern central Taiwan (Tainan County).[13] In women born before 1971 (> 15 years of age in 1986), the seronegativity rates were 0% (0 of 4), 12.8% (69 of 537), and 23% (23 of 100) in the studies reported by Wang and others,[11] Lu and others,[12] and Su and Guo,[13] respectively (Table 5).

In an effort to prevent rubella infections in all pregnant women, the Taiwanese government implemented the adult female vaccination program in 1987 to encourage childbearing women to receive vaccination. However, this immunization program was voluntary, not mandatory. In our study, we found that the susceptibility rate in women born before September 1971 was approximately 28.2%. Seronegativity in older women in our southern Taiwan study was close to the result reported by Su and Guo[13] for southern central Taiwan, but much higher than the results in Taipei. These results show a lower rate of voluntary rubella vaccination among women of childbearing age in the Pingtung area relative to those in other areas in Taiwan.[11,12]

By August 2006, 117 countries had implemented rubella vaccines as part of their routine national vaccination programs.[15,16] However, many countries in Asia such as the Philippines, Cambodia, Indonesia, and Vietnam have not introduced rubella vaccination into their national immunization program. Within the past decade, rubella vaccination programs have been introduced in some areas of China, Thailand, and Malaysia, but they have covered only parts of their populations. In 2007, there were 386 reported cases of rubella in Cambodia, 74,746 in China, 168 in Indonesia, 341 in Thailand, and 3,530 in Vietnam. Therefore, rubella infection remains endemic in many countries in Asia, and immigrants from these countries pose a new challenge in the global effort to decrease rubella infections.

A survey performed by Sathanaadan and others in Sydney, Australia, during July 1999–June 2001 found among 8,096 confinements that the rubella susceptibility rate in antenatal screening visits was 14.9% in Asian-born women and 2.2% in Australian-born women.[17] Measurements of rubella antibodies during antenatal visits at the Royal London Hospital in 2000 showed that 9% of Asian immigrants were seronegative compared with 2% of whites.[18] Another study found that 10.0% of

TABLE 5
Rubella seronegativity rates among women in different areas of Taiwan

Study, date, and location	Birth period	No. negative/total	Seronegativity (%)
Wang et al., 2004,[11] northern Taiwan (Taipei)	1971 and before	0/4	0
	After 1971	23/867	2.7
Lu et al., 2003–2005,[12] northern Taiwan (Taipei)	1971 and before	69/537	12.8
	After 1971	76/1,717	4.4
Su and Guo, 2000,[13] southern central Taiwan (Tainan)	1971 and before	23/100	23.0
	After 1971	39/985	4.0
Current study, 1999–2006, southern Taiwan (Pingtung)	August 1971 and before	442/1,568	28.2
	After August 1971	528/6,601	8.0

pregnant Asian immigrants in Catalonia, Spain, were susceptible to rubella, compared with 5.4% of pregnant women born indigenously.[19] In our study, we found that rubella seronegativity in pregnant immigrant women was 23.1%, compared with 11.9% for pregnant women born locally (Table 3). Notably, both rates are higher than those found in other international studies.

Although women who lack rubella antibodies during their antenatal visits can receive vaccinations in the post-partum period, we found that the catch-up immunization rate for rubella was only 28.6% (Table 4). Only 28.6% of women previously found without rubella antibodies might have received vaccination before their subsequent pregnancies. The results are intriguing when rates are compared for Taiwan-born (20.5%) and non–Taiwan-born (42.2%) women. Thus, immigrant women had a higher chance of seroconversion before their subsequent pregnancies. Seroconversion can occur as a result of natural rubella infection. Some women may not have reported being infected because 20–50% of rubella infections are subclinical.[20] An ideal method of calculating the catch-up immunization rate would be to obtain rubella immunization records of women having consecutive pregnancies. Unfortunately, public healthcare offices do not keep personal information of seronegative women seeking rubella immunization. Public healthcare offices keep track of only the total number of rubella vaccination offered. Therefore, it is prudent to state that we might have overestimated the catch-up immunization rate using our method and that future research is required to obtain more accurate numbers.

Nonetheless, an explanation exists for the higher rate of catch-up immunization among non–Taiwan-born women. Since the beginning of 2002, immigrant women have had to present proof of rubella immunization or positive results for rubella antibodies when applying for temporary and permanent resident status in Taiwan,[3] i.e., to qualify for legal employment and to receive social subsidies.

The low catch-up vaccination rate in Taiwan-born women presents a problem in preventing CRS. Because indigenous childbearing women do not need to apply for residency status, catch-up rubella immunization is voluntary. In Taiwan, free vaccination is available only at local government-funded health care offices. To enhance the rate of immunization, rubella vaccines should be made available at either private clinics or hospitals; they should not be restricted to government-funded health care offices.

In this study, we reviewed the seroprevalence of rubella antibodies in pregnant women over an eight-year period. Although the data originated from a single hospital, the study group was relatively representative because of the large catchment area served by this hospital and because rubella testing was a compulsory prenatal examination covered by the national health insurance system in Taiwan. Most women returned to this hospital for subsequent pregnancies because of the specialty in obstetrics care at the hospital in this geographical area. As a result, the catch-up immunization rate was relatively representative.

Our results suggest that mandatory school vaccination programs have effectively decreased the susceptibility to rubella infection, although the voluntary vaccination program in the adult female population is conducted relatively poorly in southern Taiwan. The high rates of seronegativity in immigrants from countries that lack vaccination programs should be addressed. Mandating proof of rubella immunization when immigrant women apply for their temporary and permanent residency status would help to address this problem.

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